# REMARKS

## Amendments to the Claims

Claims 1, 3, 13-21, 30, 33, and 37-39 are pending in this application. With the present submission, claim 37 has been cancelled without prejudice or disclaimer. Claims 1, 16, 20, 21, and 38 have been amended. New claims 40-50 have been added. As such, claims 1, 3, 13-21, 30, 33, and 38-50 are currently under consideration.

Specifically, claim 1 has been amended to recite: "[a] chemically modified nucleic acid molecule, wherein: a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; b) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; c) an 18 to 27 nucleotide sequence of the antisense strand is complementary to a human placental growth factor-1 (PGF-1) RNA sequence comprising SEQ ID NO: 257; d) an 18 to 27 nucleotide sequence of the sense strand is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human PGF-1 RNA sequence; e) about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications; and f) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides." Amended claim 1 finds support in the as-filed application at, for example, page 7, lines 23-29; page 10, lines 3-14 and 22-26; page 10, line 27 to page 11, line 2; page 12, lines 12-24; page 12, line 25 to page 13, line 8; page 13, lines 9-22; page 14, lines 1-6 and 14-31; page 15, lines 12-30; page 16; page 18, lines 21-28; page 19, line 1 to page 20, line 16; page 21, line 25 to page 22, line 3; page 28, line 21 to page 30, line 27; page 31, lines 10-20; page 36, line 26 to page 40, line 11; Figure 4; Tables I, II, III, & IV; and elsewhere.

Claim 16 has been amended to remove certain redundant language, without changing the scope of the claim. Claim 20 has been amended to correct an inadvertent typographic error, which does not change the scope this claim as it was previously presented. Claim 21 has been amended to substitute the term "comprises" with the term "includes," making the claim language more consistent with that of the other claims, such as claims 16 and 30, without affecting the scope of this claim.

Claim 38 has been amended so that it now depends from claim 1 rather than claim 19. Amended claim 38 finds support in the as-filed application at, for example, page 28, line 20 to page 30, line 27; and elsewhere.

New claim 40 depends from claim 1, reciting "[t]he nucleic acid molecule of claim 1, wherein the antisense strand, sense strand, or both the antisense strand and sense strand include a 3'-overhang of 1-3 nucleotides." New claim 40 finds support in the as-filed application at, for example, page 12, lines 1-11; page 17, lines 5-11; page 39, line 31 to page 40, line 4; and elsewhere.

New claim 41 depends from claim 40, reciting the nucleic acid molecule of claim 40, wherein the nucleotides of the 3'-overhang are chemically modified as specified. New claim 41 finds support in the as-filed application at, for example, page 12, lines 1-11; page 17, lines 5-11; page 39, line 31 to page 40, line 4; Figures 4-5; Tables III & IV; and elsewhere.

New claim 42 depends from claim 1, reciting the nucleic acid molecule of claim 1, further including "includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages" in one or both strands. New claim 42 finds support in the as-filed application at, for example, pages 27-30; and elsewhere.

New claim 43 depends from claim 1, reciting the nucleic acid molecule of claim 1, further including "1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more 2'-O-methoxyethyl (MOE) nucleotides" in one or both strands. New claim 43 finds support in the as-filed application at, for example, page 40, lines 17-26; page 41, lines 1-9; and elsewhere.

New claim 44 depends from claim 1, reciting the nucleic acid molecule of claim 1, further including "1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more locked nucleic acid (LNA) nucleotides" in one or both strands. New claim 44 finds support in the as-filed application at, for example, page 36, lines 18-21; page 40, lines 17-26; page 41, lines 1-9; and elsewhere.

New claim 45 is independent, reciting "[a] chemically modified nucleic acid molecule comprising a sense strand and a separate antisense strand, wherein: a) each strand of said nucleic acid molecule is independently 18 to 27 nucleotides in length; b) an 18 to 27 nucleotide sequence of the antisense strand of said nucleic acid molecule is complementary to a human placental growth factor-1 (PGF-1) RNA sequence comprising SEQ ID NO: 257; c) an 18 to 27 nucleotide sequence of the sense strand of said nucleic acid molecule is complementary to the antisense strand and comprises an 18 to

27 nucleotide sequence of the human PGF-1 RNA sequence; d) the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends; e) one or more of the nucleotides present in the sense strand and one or more of the nucleotides present in the antisense strand are 2'-O-methyl modified nucleotides; and f) one to ten or more of the pyrimidine nucleotides present in the sense strand and one to ten or more of the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides." New claim 45 finds support in the as-filed application at, for example, page 7, lines 23-29; page 10, lines 3-14 and 22-26; page 10, line 27 to page 11, line 2; page 12, lines 12-24; page 12, line 25 to page 13, line 8; page 13, lines 9-22; page 14, lines 1-6 and 14-31; page 15, lines 12-30; page 16; page 18, lines 21-28; page 19, line 1 to page 20, line 16; page 21, line 25 to page 22, line 3; page 28, line 21 to page 30, line 27; page 31, lines 10-20; page 36, line 26 to page 40, line 11; Figure 4; Tables I, II, III, & IV; and elsewhere.

New claim 46 depends from claim 45, reciting a "composition comprising the nucleic acid molecule of claim 45 in a pharmaceutically acceptable carrier or diluent." New claim 46 finds support in the as-filed application at, for example, page 22, lines 4-5; and elsewhere.

New claim 47 is independent, reciting "[a] chemically modified nucleic acid molecule, wherein: a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; b) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; c) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human placental growth factor-1 (PGF-1) RNA sequence comprising SEQ ID NO: 257; d) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human PGF-1 RNA sequence; e) at least 35% of the nucleotides of each strand of said nucleic acid molecule comprise modified nucleotides having a modification selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate, and deoxyabasic modifications; f) at least one of said modifications is a 2'-O-methyl modification; and g) at least two of said modifications are different from each other." New claim 47 finds support in the as-filed application at, for example, page 7, lines 23-29; page 10, lines 3-14 and 22-26; page 10, line 27 to page 11, line 2; page 12, lines 12-24; page 12, line 25 to page 13, line 8; page 13, lines 9-22; page 14, lines 1-6 and 14-31; page 15, lines 12-30; page 16; page 18, lines 21-28; page 19, line 1 to page 20, line 16; page 21, line 25 to page 22, line 3; page 28, line 21 to page

30, line 27; page 31, lines 10-20; page 36, line 26 to page 40, line 11; Figure 4; Tables I, II, III, & IV; and elsewhere.

New claim 48 depends from claim 47, reciting a "composition comprising the nucleic acid molecule of claim 47 in a pharmaceutically acceptable carrier or diluent." New claim 48 finds support in the as-filed application at, for example, page 22, lines 4-5; and elsewhere.

New claim 49 recites "[a] method of modulating the expression of human PGF-1 gene in a cell comprising administering the chemically modified nucleic acid molecule of claim 1 to the cell under conditions suitable for modulating the expression of human PGF-1 gene in the cell." New claim 49 finds support in the as-filed application at, for example, page 45, line 27 to page 46, line 29; and elsewhere.

New claim 50 recites "[a] method of modulating the expression of human PGF-1 gene in a cell comprising administering the chemically modified nucleic acid molecule of claim 47 to the cell under conditions suitable for modulating the expression of human PGF-1 gene in the cell." New claim 50 finds support in the as-filed application at, for example, page 45, line 27 to page 46, line 29; and elsewhere.

Amendments to and cancellation of the claims are made without prejudice or disclaimer, and do not constitute amendments to overcome any prior art or other statutory rejections. They are fully supported by the specification as filed, as explained above, and thus do not introduce new matter. Additionally, these amendments and cancellation are not and should not be construed as admissions regarding the patentability of the claimed or canceled subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims in this or in any other appropriate patent application. Accordingly, Applicants respectfully request the entry of the amendments presented.

## **Obviousness-Type Double Patenting Rejections**

Claims 1, 3, 13-21, 30, 33, and 37-39 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-35 of copending Application No. 10/922,761. Claim 37 has been canceled, rendering the rejection moot as to this claim. With respect to claims 1, 3, 13-21, 30, 33, and 38-39, Applicants reiterate that they will consider filing a terminal disclaimer when these claims are otherwise allowed.

## Rejections of Claims 1, 3, 13-21, 30, 33, and 37-39 Under 35 U.S.C. § 103(a)

Claims 1, 3, 13-21, 30, 33, and 37-39 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Carmeliet *et al.* (WO 01/85796), in view of GenBank Acc. No. NM-002632, Parrish *et al.* (Mol. Cell. Biol., 2000, 6:1077-1087), and Agrawal *et al.* (WO 94/01550 A1). Claim 37 has been canceled, rendering the rejection moot as to this claim. With respect to claims 1, 3, 13-21, 30, 33, and 38-39, Applicants respectfully traverse.

Carmeliet allegedly teaches antisense and ribozymes targeted to PIGF (PGF-1) mRNA, although the Office admitted that Carmeliet does not teach the specific nucleotide sequence encoding human PGF-1 comprising SEQ ID NO: 257, nor the use of double stranded nucleic acid having the particular modifications as recited.

Although not listed in the first paragraph of this rejection, it appears that the Office relied on the teachings of Elbashir in alleging obviousness. The previous Office Action dated December 8, 2006 cited Elbashir et al., EMBO J., 2001, 20:6877-6888, which is the reference Applicants assume was relied on in the present Office Action. Elbashir allegedly teaches siRNAs that are 21-23 nucleotides in length and mediate RNA interference. *See* Office Action, at page 3. Moreover, Elbashir allegedly teaches that "siRNAs containing nucleotide modifications known in the art such as 2'-O-methyl substitutions can stimulate RNA interference." *See id.*

Parrish allegedly teaches "that some common nucleotide modifications, including sugar modifications such as 2'-fluoro, base modifications such as 5-modified uridines and phosphorothioate backbones are tolerated in interfering RNAs." (Office Action, at pages 3-4).

Agrawal allegedly teaches self-stabilized oligonucleotides comprising an antisense portion and a self-complementary portion, resulting in a completely or partially double-stranded structure. *See* Office Action, at page 4. Moreover, Agrawal allegedly also teaches oligonucleotides including modified nucleic acid bases and/or sugars, such as 2'-O-methyl ribonucleotides.

The Office contended that one would have been motivated to combine the teachings of the cited references to successfully make chemically modified double-stranded nucleic acid molecules capable of down-regulating PGF-1 because Carmeliet allegedly teaches the use of antisense molecules as a means to antagonize the activity of PGF-1, Elbashir allegedly teaches how to make and design double stranded nucleic acid inhibitors, and Parrish allegedly teaches that sugar, base, and backbone modifications well-known and routinely used in the antisense field, are tolerated in RNA interference. *See* Office Action, at page 5.

Applicants respectfully disagree with the finding of obviousness on these bases for the reasons below.

### *a. Post-KSR Legal Framework for Obviousness*

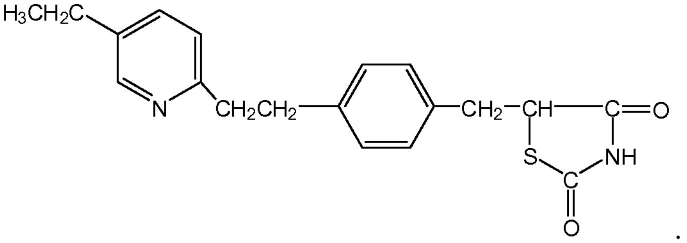
Subsequent to the filing of Applicants' last response, the Supreme Court of the United States addressed the legal standards for determining obviousness under 35 U.S.C. § 103 in *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007).

At the outset, reaffirming the objective standard for obviousness set forth in *Graham v. John Deere Co. of Kansas City* (383 U.S. 1, 17-18 (1966)), the *KSR* Court held that the teaching-suggestion-motivation test ("the TSM test") devised by the Federal Circuit Court of Appeals, if not applied in a rigid and mandatory fashion, is consistent with the *Graham* analysis. *KSR,* at 1731. Therefore, arguments and submissions regarding obviousness in Applicants' prior response, which did not follow the TSM test framework rigidly, are still valid post *KSR*.

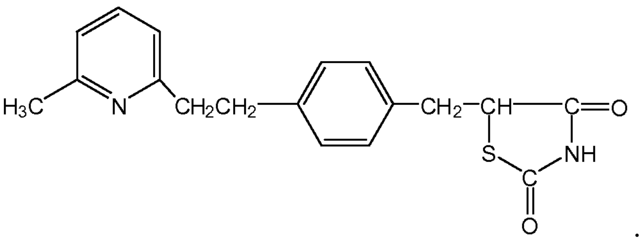
The *KSR* decision focused on how to determine obviousness when all elements of a claimed invention can be found in the prior art. Recognizing that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known," (*KSR*, at 1741), the Supreme Court emphasized three factors: (1) whether there is an "apparent reason to combine the known elements in the fashion claimed by the patent at issue," *id.* at 1740-41; (2) whether, when known elements are combined, there is predictability of yielding the claimed results; and (3) whether the prior art teaches away from modifying known elements in such a way that would lead to the claimed invention. The Court found obviousness in *KSR* because "there is a design need or market pressure to solve a problem [*i.e.,* a reason] and there are **a finite number** of **identified, predictable** solutions." *See id,* at 1732 (*emphasis added*). The *KSR* Court emphasized the importance of using teaching-away references to guard against hindsight reconstruction, stating that "[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). As such, teaching away is significant not only in undermining the reason(s) for making a claimed invention, but also in diminishing the predictability of whether a combination of prior art elements may be successful. As discussed below, the prior art to the instant invention does just that, not only teaching away from making the claimed invention, but also suggesting the lack of predictability.

These factors have subsequently been interpreted by the Federal Circuit on several occasions. For example, applying the framework of *KSR,* the Federal Circuit held it necessary to demonstrate that the prior art provide reasons to make the particular invention and not merely general guidance before finding obviousness in *Pharmastem Therapeutics v. Viacell,* 83 U.S.P.Q.2d 1289, 1350 (Fed. Cir. 2007) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)), and stating that "an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."). Therefore, the mere fact that certain approaches can be undertaken does not constitute a legally sufficient reason to combine the known elements in an obviousness inquiry.

*Takeda Chemical Industries v. Alpharma,* 2007 WL1839698, *15 (Fed. Cir. June 28, 2007), further illustrates the importance of having a finite number of identified, predictable solutions for a finding of obviousness. In *Takeda*, the claim at issue was directed to the compound pioglitazone, wherein an ethyl group is attached to the 5'-position of a pyridyl ring:



The alleged infringer argued that the claim at issue was obvious over the prior art compound b, which includes a pyridyl ring with a methyl group attached at the 6'-position:



The Federal Circuit agreed with the district court's finding of nonobviousness, despite the fact that the claimed compound differs from the alleged prior art compound in merely two aspects: (1) the type of substituent (methyl in compound b vs. ethyl in the claimed compound); and (2) the location of the substituent (at the 6-position on the pyridyl ring in compound b vs. at the 5-position in the claimed compound). The Federal Circuit found that the prior art would not have first led one of ordinary skill in the art to select compound b as a lead compound for investigation, and then led that person to make two obvious chemical changes: replacing a methyl group with an ethyl group, and "ring-walk" the ethyl group to the 5'-position, despite the fact that compound b was disclosed in a prior art reference. The Federal Circuit called attention to the fact that the reference disclosed hundreds of millions of other compounds in the same family, and exemplified 54 of those compounds, including compound b, but was silent as to which of those compounds would have the desired properties. The Federal Circuit also found it important that another reference also disclosed compound b, but did not identify it as one of the three most favorable compounds, and in fact singled it out as one having prominent undesirable side effects. On these facts, the Federal Circuit approved the district court's finding that a person of ordinary skill in the art would not have selected compound b as a lead compound.

The Federal Circuit then rejected the contention that, under *KSR*, it would have been obvious to pick compound b and modify it as claimed because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." According to the Federal Circuit, this was not a situation when there are a finite number of identified and predictable solutions to a problem. Instead, compound b "exhibited negative properties that would have directed one of ordinary skill in the art away from that compound." *Id.* at *15. Thus, the Federal Circuit concluded, "this case fails to present the type of situation contemplated by the [*KSR*] Court when it stated that an invention may be deemed obvious if it was 'obvious to try.'" *Id.*

The defendant's reliance on *Pfizer v. Apotex, Inc.,* 480 F.3d 1348 (Fed. Cir. 2007) fared no better. Contrasting *Pfizer*, where obviousness was found because the prior art teaches how to narrow the possibilities of a large family of lead compounds to a group of efficacious ones, the Federal Circuit pointed to the district court's finding of nothing in the prior art to narrow the possibilities of millions of lead compounds to compound b in *Takeda.*

The Federal Circuit went on to state that even if the prior art would have led to the selection of compound b as the lead compound, the obviousness argument failed on a second ground. The Court found nothing in the prior art to suggest making the specific molecular modification to compound b that would lead to the claimed compounds. The Court also pointed out that studies have confirmed that several other compounds, "and one compound in particular, compound 99, that had no identified problems" in properties "differ significantly from compound b in structure." *Id.* at *18. The Court concluded that the process of modifying lead compounds was not routine at the time of the invention because of the great number of possible modifications, and because there was no way of predicting which of the modifications might bring about desired properties, especially in view of the fact that similar modifications did not always yield similar changes in properties. Therefore, there is no *prima facie* obviousness even when a general approach to a problem is known, if that general approach yields numerous choices, and the prior art does not help to predict which of those choices would be more efficacious.

*Takeda* also illustrates how a prior art reference teaching away from the claimed invention may further buttress the want of predictability. Specifically, evidence in the prior art that certain modifications produce undesirable properties should be taken as not only leading a skilled artisan away from those particular modifications, but also as suggesting the lack of predictability on how similar modifications may fare. In other words, if the prior art teaches that certain modifications sometimes but not always give rise to the desired properties, there is no way of predicting what other similar modifications may do.

### ***b. The Cited References***

Applying the post-*KSR* framework, Applicants respectfully submit that the cited reference taken together do not provide a reason that would have compelled a skilled person in the art to modify a double stranded construct such as the one recited in the instant claims. Nor do they teach that skilled person how to narrow down or predict which of the exceedingly large number of potential modified constructs may retain RNAi activities. Thus, the cited references do not render the instant claims *prima facie* obvious.

#### *(1) No compelling reason to modify the claimed double stranded constructs.*

Applying the post-*KSR* framework, Applicants submit that, at the time of the present invention, there was no reason for a skilled artisan to apply the chemical modifications of single stranded nucleic acid molecules to double stranded RNA molecules. In fact, at the time of the present invention, it was believed that dsRNA were substantially more stable than single stranded nucleic acid constructs, such as antisense and ribozyme oligonucleotides, and were therefore in need of little, if any, modification.

Additionally, Applicants respectfully submit that the Office has not satisfactorily explained why it would be within the purview of those ordinarily skilled in the art at the time of the present invention to find a reasonable expectation of success in modifying double stranded nucleic acid molecules of the claimed length, using the specified chemical modifications and patterns, and modifying these molecules to the claimed extent. Contrary to the Office's allegation that Elbashir teaches that "siRNAs containing nucleotide modifications known in the art such as 2'-OMe substitutions can stimulate RNA interference", Elbashir expressly teaches that extensive chemical modifications of dsRNA, particularly 2-deoxy and 2-O-methyl modifications, abolish RNAi activity and are thus not well tolerated on one or both strands. The Elbashir reference actually indicates the mindset of those skilled persons at the time, as evidenced by numerous research publications that came soon thereafter. Those publications uniformly suggested that skilled artisans followed the teachings of Elbashir *et al.,* and designed siRNA molecules without any modifications other than the 2'-deoxythymidine nucleotides at the 3'-end of the siRNA. *See, e.g.,* Bitko *et al.*, 2001, BMC Microbiology, 1 (34), page 9, left column, "Materials and Methods;" Kuman *et al.,* 2002, Malarial Journal, 1(5), page 9, right column, "Transfection by Inhibitory dsRNA;" and Holen *et al.,* 2002, Nucleic Acid Research, 30, pages 1757-66, Figures 1, 2, and 6. Accordingly, regardless whether the Office now has been motivated by the cited references, which is irrelevant in the obviousness inquiry, those skilled persons were **in fact** led down a directly opposite path from the one taken by Applicants.

Furthermore, Parrish teaches that modification of cytidine to deoxycytidine on either the sense strand or the antisense strand leads to reduced interference activity. *See* Parrish, at page 1081, right column ("Modification of cytidine to deoxycytidine … on either the sense strand or the antisense strand of the trigger was sufficient to produce a substantial decrease in interference activity."). It simply defies logic to suggest that, because the siRNA prior art teaches that certain experiments have failed, it motivates those skilled in the art to repeat the same experiments until they are successful. The teachings of Elbashir and Parrish should alone be sufficient to indicate that Elbashir and Parrish give no reason to modify double stranded nucleic acid constructs, at least when it comes to using 2'-O-methyl modifications and certain 2'-deoxy-2'-fluoro modifications.

Accordingly, the Office has not established a compelling reason to make modified double stranded nucleic acid molecules as claimed, let alone the extensively modified constructs of the present claims.

*(2) No teaching as to which of modified molecules would be active.*

More importantly, however, even assuming the skilled artisans would find a reason to modify double stranded RNA constructs with the chemical modifications that had been used with antisense or ribozyme molecules, potentially hundreds of thousands, if not more, prospective chemical modification patterns may be generated in a double stranded nucleic acid molecule that is 18 to 27 nucleotides long. The cited references are either silent as to which of the modified molecules might be efficacious, or teach away from making certain types of modifications. Thus, the problem faced by Applicants at the time of the invention did not have "a finite number of identified, predictable solutions," and the instant claims are accordingly not *prima facie* obvious.

The Office alleged that "Elbashir et al. and Parrish et al. each teach that interfering RNAs containing [sugar, base, and backbone] modifications are active in provoking RNA interference." Office Action, at page 5. Applicants submit, however, that this statement indicates a superficial and inaccurate reading of both Elbashir and Parrish. More accurately read, Parrish teaches (and especially in Figure 5) the modifications of unc-22A constructs that are 742 nucleotides long. *See* Parrish, at page 1081, left column, in the text accompanying Figure 5 ("2-fluorouracil, 2'-aminouracile, 2'-deoxythymidine, and 2'-deoxy-cytidine were incorporated **into individual strands of the 742 nt unc-22A segments** using T3 and T7 polymerases (Experimental Procedures)") *(emphasis added)*). Moreover, Parrish describes 2'-deoxy-2'-fluoro uridine modifications but not 2'-deoxy-2'-fluoro cytidine modifications, in fact stating that 2'-deoxy modifications of cytidine is not tolerated. *See* Parrish, at page 1081, right column ("Modification of cytidine to deoxycytidine … on either the sense strand or the antisense strand of the trigger was sufficient to produce a substantial decrease in interference activity."). Furthermore, Parrish describes 2'-deoxy-2'-fluoro modification of uridine in either the sense strand or the antisense strand, but never simultaneously in both strands. *See e.g.,* Parrish, at page 1081, left column, Figure 5B (describing that interference activities of unc-22 were retained with a 2'-uracil → 2'-fluorouracil in the sense strand, and unmodified RNA antisense strand; or with an unmodified RNA sense strand and a modified uracil → 2'-fluoro uracil antisense strand). Therefore, Parrish does not inform the selection of a double stranded nucleic acid molecule of the claimed length, let alone the specific types, patterns and levels of modifications as claimed. Indeed, Parrish can be said to teach away from 2'-deoxy modifications of cytidine, therefore teaching away from the use of 2'-deoxy-2'-fluoro pyrimidine modifications, as recited in the instant claims.

Moreover, Elbashir expressly teaches that 2'-deoxy modification beyond the terminal residues and 2'-O-methyl modifications anywhere on a short, double stranded nucleic acid molecule substantially reduce or completely abrogate the RNAi activities. In particular, Elbashir expressly states that:

> 2'-deoxy substitutions of the 2 nt 3' overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-*O*-methyl modifications, reduce the**

> **ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNAP assembly.**

*See* page 6885 (*emphasis added*). Applicants note that the term "[m]ore extensive" in the second sentence could have only been intended to modify the term "2'-deoxy" and not the term "2'-O-methyl," because the first sentence does not refer to "2'-O-methyl" at all. This conclusion is also supported by the fact that all 2'-O-methyl modified siRNA in the experimental data were inactive constructs. Based on such express teaching, then, it is unclear how Elbashir could have taught or suggested those skilled in the art to make the extensively chemically modified double stranded nucleic acid molecules of the instant claims. What is clear, however, is that Elbashir does nothing to narrow the hundreds of thousands or more potential types, positions, and/or levels of chemical modifications that may take place in a double-stranded nucleic acid molecule wherein each strand is 18 to 27 nucleotides long. Elabshir further teaches that some of those patterns involving internal modifications (*i.e.,* beyond the terminal modifications) may be active while others may not be, but does nothing to inform or predict which specific pattern(s) will more likely be active and which will not.

Agrawal allegedly teaches 2’-O-methyl ribonucleotides and 3’ caps in self-stabilized oligonucleotides. However, Agrawal fails to teach the selection of a double stranded nucleic acid molecule of the claimed length, and does not teach the specific types, patterns and levels of modifications as claimed, and the Office does not so allege.

In fact, the cited references, taken together indicates to those skilled in the art that there was no way of predicting what specific position(s), level(s), or type(s) of chemical modifications amongst the hundreds of thousands or more of potential modification patterns would lead to a "successful" RNA duplex that is capable of mediating RNA interference. Therefore, not unlike the situation in *Takeda,* because of the great number of possible modifications on a 18 to 27 nucleotide long duplex, and because there was no way of predicting which of the modifications might bring about a molecule with RNAi activity, the cited references do not render the instant claims obvious.

For the reasons set forth above, the cited references do not render the instant claims obvious. Accordingly, Applicant respectfully requests the withdrawal of the rejections under 35 U.S.C. § 103.

## Conclusion

In view of the foregoing remarks, Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: October 31, 2007

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